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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/693,204	10/19/2000	Janet A. Warrington	3240.1	7262
22886	7590	04/01/2004	EXAMINER	
AFFYMETRIX, INC ATTN: CHIEF IP COUNSEL, LEGAL DEPT. 3380 CENTRAL EXPRESSWAY SANTA CLARA, CA 95051			JOHANNSEN, DIANA B	
			ART UNIT	PAPER NUMBER
			1634	

DATE MAILED: 04/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/693,204

Applicant(s)

WARRINGTON ET AL.

Examiner

Diana B. Johannsen

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12 and 13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12 and 13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on August 26, 2003 (a duplicate copy of which was provided on February 25, 2004) has been entered.
2. Claims 10-11 have been canceled. Claims 12-13 have been amended, and are now under consideration.

Specification

3. The use of the trademarks GENECHIP, GENEARRAY, UNIGENE, and GENBANK has been noted in this application. The trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims have been amended so as to require a step of "measuring the expression of said gene in said plurality of samples and simultaneously measuring the expression of at least ten maintenance genes" (see lines 3-4 of claim 13). However, the specification as originally filed does not provide basis for such a step. Particularly, the specification does not disclose or exemplify a method for "determining the expression of a gene" in which the expression of the gene and the expression of at least ten maintenance genes are simultaneously measured and then compared. It is noted that the passages in the specification which are identified by Applicant as providing support for this amendment do not provide basis for the recitation of the term "simultaneously" in the claims; further, the examiner could not locate support for this recitation elsewhere in the specification. Accordingly, the originally-filed specification does not provide support for Applicant's amendments.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-13 are indefinite because it is unclear as to whether the claims are drawn to a method of "determining the expression of a gene in a plurality of biological samples" as recited in the preamble of claim 13, or to a method of comparing expression of a gene in a plurality of samples, as recited in the final process step of the claim. The claims as written do not make clear how the step of comparing relates to or results in "determining the expression of a gene." Clarification is required.

Claim 12 is indefinite over the recitation of the limitations "the expression measurement of said gene" and "the expression measurement of said maintenance genes" because there is insufficient antecedent basis for these limitations in the claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacLeod et al (U.S. Patent No. 6,221,600 B1 [4/2001; filed 10/8/1999]) in view of Kagawa et al (Int. J. Biochem. 20(3):219-29 [1990]).

It is first noted that the instant claims are not limited to, e.g., a particular set of "maintenance genes" with which unexpected results were obtained. It is also noted that the specification discloses at pages 7-8 that "In this application, housekeeping genes are also referred to as maintenance genes."

MacLeod et al disclose methods in which a "set of genes is identified whose expression is relatively constant among different biological samples," which genes are "usually comprised of 'housekeeping' genes" (col 38, lines 35-46). MacLeod et al disclose the use of such sets of genes as "sets of control or standardization genes" in methods of monitoring and quantitating variations in gene expression among different tissue types (see entire reference). MacLeod et al disclose that expression of genes of interest is compared with expression of the set of standardization genes, and exemplify the calculation of expression ratios (see, e.g., col 38, lines 42-44, and Example 2). MacLeod et al teach that expression of genes of interest is "normalized...by the use of sets of control or standardization genes" (col 38, lines 35-36), and therefore teach a method in which maintenance gene expression is used "as a control to normalize the expression" of a gene or genes of interest, as required by the claims. Additionally,

MacLeod et al disclose the simultaneous analysis of multiple samples (see, e.g., col 4, lines 54-55), and the simultaneous analysis of both genes of interest and a set of housekeeping genes (see col 38, lines 42-44, where MacLeod et al state that amplifications for maintenance genes are performed “in parallel” with amplifications of genes of interest, as well as Example 2). MacLeod et al teach sets of housekeeping genes comprising at least 10 members (see, e.g., Table 4); however, MacLeod et al do not disclose measuring at least ten of the particular maintenance genes recited in claim 13. Kagawa et al disclose that ATP synthases are encoding by multiple genes, and that genes encoding ATP synthases are considered by those of skill in the art to constitute housekeeping genes (see entire reference, especially p. 219-220). It is noted that while Applicant has amended the claims to delete the general recitation of “ATP synthase,” claim 13 recites 10 genes encoding subunits of ATP synthases (specifically, “ATP synthase subunit c encoded by P1,” “ATP synthase alpha subunit,” “Vacuolar ATP synthase subunit AC45 precursor,” “ATP synthase gamma-subunit (L-type),” “ATP synthase beta subunit,” “Mitochondrial ATPase coupling factor 6,” “NaK-ATPase beta-1 subunit,” “Sodium/potassium-transporting ATPase beta-3 subunit,” “H⁺-ATP synthase subunit b,” and “Vacuolar-type H⁽⁺⁾-ATPase 115 kDa subunit”). In view of the teachings of Kagawa et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of MacLeod et al so as to have employed therein a set of control genes comprising any gene encoding an ATP synthase subunit, including the particular genes recited in the instant claims. While MacLeod et al exemplify a few particular sets of control genes, MacLeod et al indicate

that those sets are “examples” (see col 38, lines 44-46), and MacLeod et al’s teachings encompass the use of sets of genes “whose expression is relatively constant among different biological samples,” which sets are “usually comprised of ‘housekeeping’ genes” (see col 38, lines 38-42). Accordingly, absent a showing of unexpected results with a particular set of known housekeeping genes, it would have been obvious to one of ordinary skill in the art to have employed any set of such genes – including a set comprising any genes encoding subunits of ATP synthases - as a control in the methods of MacLeod et al. An ordinary artisan would have been motivated to have employed genes encoding ATP synthase subunits whenever those genes were readily available to the artisan, for the advantage of convenience.

Regarding the rejection of claims 10-13 over MacLeod et al in view of Kagawa et al set forth in the Office action of August 28, 2002, Applicant states in the Remarks of August 26, 2003 that “Kagawa et al discuss ATP synthesis and disclose that although ATP synthase and oligomers supplying energy to F_0F_1 are housekeeping, they are under a coordinated transcriptional control mechanism and their expression may be closely related to cell differentiation (see Abstract, paragraphs 4 and 6),” and argues that “Thus, Kagawa et al teaches that they may not behave like typical housekeeping genes.” This argument has been thoroughly considered but is not persuasive. While the Abstract paragraphs noted by Applicant do indicate that “ATP synthase (F_0F_1) and these oligomers supplying energy to F_0F_1 are under some coordinated transcriptional control,” the reference also clearly teaches that genes encoding ATP synthase “are housekeeping” (see paragraph 4 of Abstract), and nothing in the

MacLeod et al reference suggests, e.g., that certain housekeeping genes would be unsuitable for use in their methods simply because those genes are under coordinated transcriptional control. Therefore, Applicant's argument is not persuasive.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Diana B. Johannsen
Patent Examiner
March 26, 2004